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[Intervention Review]

Interventions for erythropoietin-resistant anaemia in dialysis patients

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ABSTRACT

Background

People living with end-stage kidney disease (ESKD) often develop anaemia. Erythropoiesis-simulating agents (ESAs) are often given to people living with ESKD to maintain haemoglobin at a level to minimise need for transfusion. However, about 5% to 10% of patients with ESKD exhibit resistance to ESAs, and observational studies have shown that patients requiring high doses of ESA are at increased risk of mortality.

Objectives

This review aimed to study the effects of interventions for the treatment of ESA-resistant anaemia in people with ESKD.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE for randomised controlled trials (RCT) that involved participants with ESKD on dialysis or who were pre-dialysis patients with chronic kidney disease (stage 5). Date of last search: April 2013.

Selection criteria

ESA resistance was defined as failure to achieve or maintain haemoglobin/haematocrit levels within the desired target range despite appropriate ESA doses (erythropoietin ≥ 450 U/kg/wk intravenously or ≥ 300 U/kg/wk subcutaneously; darbepoetin ≥ 1.5 µg/kg/wk) in people who were not nutritionally deficient, or who had haematological or bleeding disorders. Extended inclusion criteria for ESA hyporesponsive state were: erythropoietin dose ≥ 300 U/kg/wk and ≥ 150 U/kg/wk for intravenous administration; or ≥ 200 U/kg/wk and ≥ 100 U/kg/wk for subcutaneous administration; or darbepoetin dose ≥ 1.0 µg/kg/wk).

Data collection and analysis

Two authors independently assessed study quality and extracted data. Statistical analyses were performed using a random effects model and results expressed as risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CI).

Main results

Titles and abstracts of 521 records were screened, of which we reviewed 99 from the full text. Only two studies matched our inclusion criteria. One study compared intravenous vitamin C versus no study medication for six months in 42 ESKD patients on haemodialysis who required intravenous erythropoietin (dose $\geq$ 450 U/kg/wk). The other included study compared high-flux dialyser versus low-flux dialyser for six months in 48 haemodialysis patients who required subcutaneous erythropoietin (dose $\geq$ 200 U/kg/wk). Because interventions differed, data could not be combined for quantitative meta-analysis.

Authors' conclusions

There was inadequate evidence identified to inform recommendation of any intervention to ameliorate ESA hyporesponsiveness. Adequately powered RCTs are required to establish the safety and efficacy of interventions to improve responsiveness to ESA therapy.

PLAIN LANGUAGE SUMMARY

Interventions for anaemia in dialysis patients who are resistant to erythropoietin

Many people with chronic kidney disease (CKD) who are on dialysis develop anaemia (too few or poor quality red blood cells). Drugs in the erythropoiesis-stimulating family increase the production of red blood cells to resolve anaemia. Although ESAs have been highly beneficial for many, about 10% of people get either low or no benefit from treatment. Inability to control and stabilise anaemia can lead to poor rates of survival and increased risk of stroke so it is important to find effective treatment to manage anaemia in people who do not respond adequately to ESA therapy.

We searched the literature to find evidence about how best to treat people who do not benefit from ESA treatment. We found two studies: one that assessed intravenous vitamin C and another that looked at high-flux dialyser fluids as possible therapies. These studies were small (total of 90 participants) and were selective: they included haemodialysis, but not peritoneal dialysis, patients. This meant that the results of these studies could not be applied to all people with CKD on dialysis who were receiving ESA therapy. The lack of evidence meant that we could not determine or recommend an alternate treatment for people who do not respond to ESA.

More powerful and rigorous studies are needed to systematically assess all therapies that are aimed to treat people who do not respond to ESA therapy. Until such evidence is available, no therapy can be confidently recommended for this problem.

BACKGROUND

Description of the condition

Erythropoiesis-stimulating agents (ESAs) are perhaps the most rigorously tested group of drugs in nephrology. Since the introduction of ESAs, there have been substantial reductions in blood transfusion requirements among patients living with chronic kidney disease (CKD) (Eschbach 1989).

A systematic review of 14 randomised controlled and uncontrolled trials in pre-dialysis CKD patients demonstrated that treatment of anaemia with ESAs improved energy levels and physical function (Gandra 2010). Unfortunately, a considerable proportion of these patients exhibited suboptimal haematologic response to ESA (Benz 1999; Valderrabano 1996).

There are several known causes of suboptimal response to ESA. These include deficiencies in iron, vitamin B_{12}, and folate; infection, chronic inflammatory state, neoplasia, severe hyperparathyroidism, aluminium intoxication, inadequate dialysis, myelosuppressive agents, haemoglobinopathies, myelodysplasia and antibody-mediated pure red cell aplasia (Macdougall 2002). However, after excluding these conditions it was found that about 10% of patients exhibit ESA-resistant anaemia, and these people have greatly increased rates of morbidity and mortality (Kausz 2005; Macdougall 2002; Zhang 2004).

ESA treatment used to target high haemoglobin levels in people with CKD is associated with deleterious (Phrommintikul 2007) or neutral (Palmer 2010) impacts on survival and increased risks of stroke, vascular access thrombosis and hypertension without any reduction in cardiovascular events (Palmer 2010; Phrommintikul 2007).

Although RCTs and systematic reviews consistently show more harm than benefit associated with higher haemoglobin targets for ESA treatment (Besarab 1998; Palmer 2010; Pfeffer 2009; Phrommintikul 2007; Singh 2006), secondary analyses of RCTs and observational studies have demonstrated that poor response to ESA treatment rather than achieved high haemoglobin, may be responsible for the observed suboptimal outcomes in people with CKD (Kilpatrick 2008; Messana 2009; Regidor 2006; Solomon 2010; Szczech 2008).

These studies also showed that patients who required higher doses of ESA experienced increased mortality at any haemoglobin level, and that patients who achieve target haemoglobin levels had better outcomes than those who did not (Badve 2011). Therefore, therapies targeting ESA resistance could be a promising treatment strategy in CKD anaemia management.

Description of the intervention

Although there is no effective treatment for patients with ESA-resistant anaemia at present, a number of interventions such as L-carnitine, ascorbic acid, oxpentifylline, androgens and statins have been investigated.

OBJECTIVES

This review looked at the benefits and harms of any intervention used in the treatment of ESA-resistant anaemia in people with end-stage kidney disease (ESKD) who were receiving dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at interventions for the treatment of ESA-resistant anaemia in people with ESKD were included in our review.

Types of participants

- Adults and children with ESKD (chronic kidney disease (CKD) stage 5 or pre-dialysis) or those receiving dialysis (either haemodialysis or peritoneal dialysis).
- Adults and children with ESKD receiving any type of ESA for anaemia (anaemia defined as haemoglobin < 110 g/L or as defined by the investigators).
- Evidence of ESA resistance, defined as failure to achieve or maintain target range haemoglobin/haematocrit levels in spite of appropriate ESA doses (erythropoietin ≥ 450 U/kg/wk intravenous administration or ≥ 300 U/kg/wk for subcutaneous administration or darbepoetin ≥ 1.5 µg/kg/wk) (KDOQI 2001; Locatelli 2004). This inclusion criterion was amended after publication of the protocol of this systematic review because only one eligible study was found. Extended inclusion criteria were studies that defined ESA-hyporesponsive state as failure to achieve or maintain target haemoglobin/haematocrit in spite of the following doses of the ESA: erythropoietin dosage ≥ 300 and ≥150 U/kg/wk for IV administration; or ≥ 200 and ≥100 U/kg/wk for subcutaneous administration; or darbepoetin dosage ≥ 1.0 µg/kg/wk).
- All known causes of ESA-resistance (such as iron deficiency, vitamin B_{12} deficiency, folate deficiency, infection, chronic inflammatory state, neoplasia, severe hyperparathyroidism, aluminium intoxication, inadequate dialysis, myelosuppressive agents, haemoglobinopathies, myelodysplasia and antibody-mediated pure red cell aplasia) must have been ruled out.
- Studies performed in kidney transplant recipients were excluded.

Types of interventions

Any potential intervention used to treat ESA-resistance, such as L-carnitine, ascorbic acid, oxpentifylline, androgens, and statins, were included in this review.

Types of outcome measures

- All-cause mortality
- Cardiovascular mortality
- Non-fatal cardiovascular events
- Number of patients achieving target haemoglobin/haematocrit
- Difference or changes in haemoglobin or haematocrit between intervention and control groups at study end
- Difference or changes in ESA dose between intervention and control groups at study end
- Blood transfusion requirements
- Quality of life
- Hospitalisation
- Any reported adverse events
- Differences or changes in inflammatory biomarkers between intervention and control groups at study end
- Differences or changes in biomarkers of oxidative stress between intervention and control groups at study end.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's specialised register 18th March 2013 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.
The Cochrane Renal Group's Specialised Register contains studies identified from:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the specialised register are identified through search strategies for CENTRAL, MEDLINE and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the specialised register section of information about the Cochrane Renal Group. See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines, review articles and relevant studies.
2. Relevant missing or incomplete or unpublished data from the clinical studies were requested from the respective investigators/ authors by written correspondence.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies relevant to the review. Titles and abstracts were screened independently by three authors, who discarded studies that were not applicable. However, studies and reviews that potentially included relevant data or study information were retained initially. The same three authors independently assessed retrieved abstracts, and if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals was to be translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes were only published in earlier versions, these data were used. Any discrepancies between published versions was to be highlighted. Disagreements were resolved by consensus.

Assessment of risk of bias in included studies

The following items will be independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel
    - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, cardiovascular mortality, non-fatal cardiovascular events, number of patients achieving haemoglobin/haematocrit targets, number of patients requiring hospitalisation, number of patients requiring blood transfusions, number of patients with medication-related adverse effects), results were expressed as risk ratios (RR) with 95% confidence intervals (CI). For continuous data (haemoglobin, haematocrit, iron studies, ESA dosage, iron dosage, hospitalisation days, quality of life scores, inflammatory biomarkers, biomarkers of oxidative stress), results were expressed as mean difference (MD).

Dealing with missing data

We planned that any further information required from the original author was to be requested by written correspondence, and any relevant information obtained was be included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat (ITT), as-treated and per-protocol (PP) population was performed.

Assessment of heterogeneity

Heterogeneity was to be analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Data synthesis

Data were to be pooled using the random-effects model.

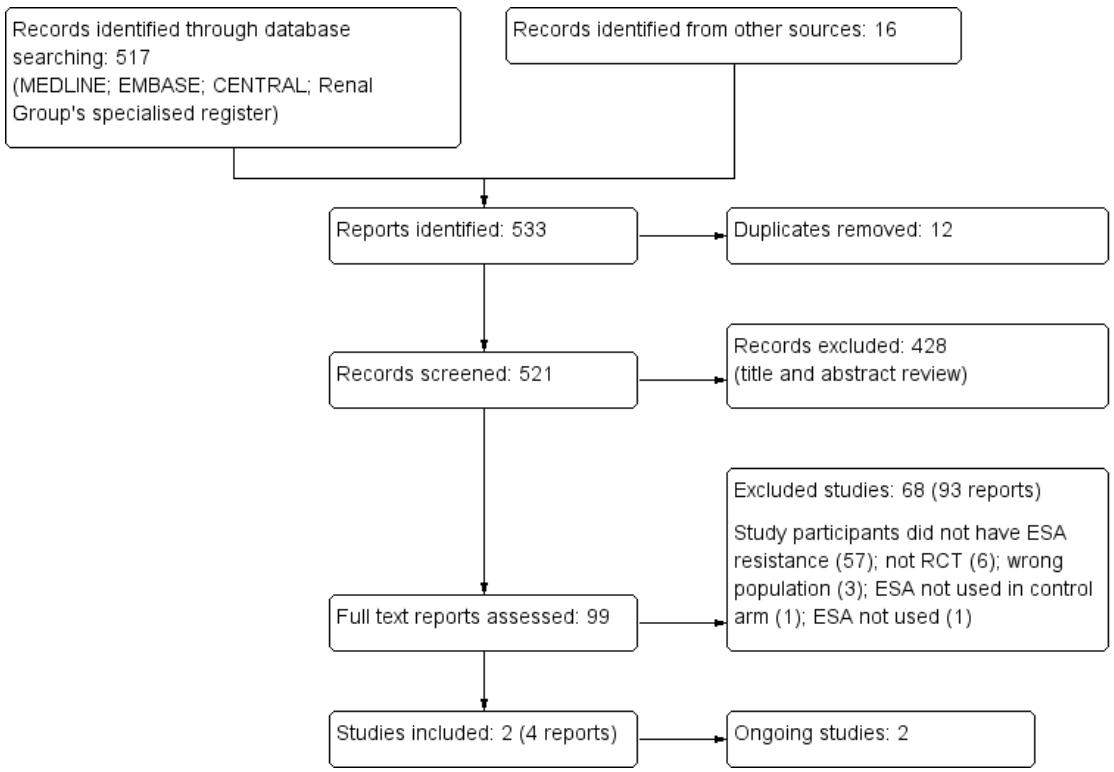
RESULTS

Description of studies

Results of the search

We identified 533 abstracts using the search strategy described (Figure 1). After screening titles and abstracts, 99 reports were selected for full text review. Only two studies (Attallah 2006; Ayli 2004) met our inclusion criteria, and of these, one investigated our extended inclusion criterion of ESA hyporesponsive state (Ayli 2004).

Figure 1. The PRISMA flow chart showing selection of studies



We considered inclusion of a study that applied our extended inclusion criterion of ESA-hyporesponsive state (Sezer 2002). In this study, participants in both arms received the investigational drug (vitamin C) in the first study phase (eight weeks). Non-responders were excluded at the end of the first phase. During the second phase, remaining participants were randomised to receive either the investigational drug at a reduced frequency or no study drug for another eight weeks. Since the investigators did not define 'non-responder', and there was a strong possibility of carry over effect of vitamin C administered before randomisation, the study was excluded from this systematic review.

Included studies

Two studies met our inclusion criteria.

- Attallah 2006 enrolled 42 haemodialysis patients and compared IV vitamin C given at each dialysis session to no treatment.
- Ayli 2004 enrolled 48 haemodialysis patients and compared high-flux versus low-flux dialysis membranes

Excluded studies

We excluded 68 studies after full-text review: six were not randomised; 58 included participants who did not have ESA resistance; two included iron deficient participants who lacked true ESA resistance; and two studies did not use ESA in the control arm.

Risk of bias in included studies

Allocation

Allocation concealment was unclear in both included studies (Attallah 2006; Ayli 2004).

Blinding

It was unclear if in Attallah 2006, an open-label study, outcome assessors were blinded. Likewise, blinding of participants, investigators or outcome assessors in Ayli 2004 was also unclear.

Incomplete outcome data

All participants were followed for the entire study period and accounted for in both studies. Attrition bias arising from incomplete outcome reporting was deemed to be low risk.

Selective reporting

Neither study reported proportions of participants in each study arm who achieved haemoglobin target levels. The risk of reporting bias in both was therefore unclear.

Other potential sources of bias

Both studies were judged to be at high risk of other potential sources of bias due to single-centre study design and exclusion of patients on peritoneal dialysis.

Effects of interventions

Treatments differed in the interventional arms of Attallah 2006 and Ayli 2004 (vitamin C and high-flux dialyser). Therefore, data were not combined and results are presented separately.

Clinical outcomes

All-cause and cardiovascular mortality

No deaths were reported in either study.

Non-fatal cardiovascular events

Attallah 2006 reported no significant difference in the risk of non-fatal cardiovascular events between study arms (Analysis 1.1: RR 0.79, 95% CI 0.20 to 3.09).
Ayli 2004 did not report non-fatal cardiovascular events.

Participants achieving target haemoglobin or haematocrit

Neither study reported the proportions of participants who achieved target haemoglobin or haematocrit levels.

Requirement of blood transfusions

Attallah 2006 reported no participants included in the final analysis required blood transfusion. However, one participant from the control group was excluded from the final analysis because of the need for a blood transfusion due to a significant upper gastrointestinal bleed.
Ayli 2004 did not report need for blood transfusion.

Hospitalisations

Attallah 2006 reported no significant difference in the risk of hospitalisations between the groups (Analysis 1.2: RR 0.96, 95% CI 0.56 to 1.66).
Ayli 2004 did not report hospitalisations.

Medication-related adverse events

Attallah 2006 reported there were no adverse events noted in either group. Ayli 2004 did not report adverse events.

Haematology and biochemistry results

Haemoglobin

Both studies reported significantly higher haemoglobin levels in the treatment groups compared to the control groups (Analysis 2.1.1: MD 0.9 g/dL, 95% CI 0.38 to 1.42; Attallah 2006); (Analysis 2.1.2: MD 1.9 g/dL, 95% CI 1.64 to 2.16; Ayli 2004).

Haematocrit

Attallah 2006 did not report data on participants' haematocrit levels. Ayli 2004 reported that among interventional arm participants haematocrit was significantly higher than those in the control arm (Analysis 2.2: MD 6.8%, 95% CI 5.67 to 7.93).

Transferin saturation (TSAT)

Attallah 2006 reported that TSAT was significantly higher in interventional than control arm participants (Analysis 2.3.1: MD 8.00%, 95% CI 6.22 to 9.78). There was no significant difference in TSAT between study arms reported by Ayli 2004 (Analysis 2.3.2: MD 1.30%, 95% CI -3.99 to 6.59).

Ferritin

Attallah 2006 reported that ferritin was significantly higher among interventional than control arm participants (Analysis 2.4.1: MD 8.00 ng/mL, 95% CI -85.51 to 101.51). There was no significant difference between study arms reported by Ayli 2004 (Analysis 2.4.2: MD -3.00 ng/mL, 95% CI -43.46 to 37.46).

Haemoglobin content in reticulocytes (CHr)

Attallah 2006 reported that CHr was significantly higher in interventional than control arm participants (Analysis 2.5: MD 0.90 pg, 95% CI 0.40 to 1.40). Ayli 2004 did not report CHr data.

Inflammatory biomarkers: C-reactive protein

Attallah 2006 reported C-reactive protein was significantly lower in vitamin C group compared to the control group (Analysis 2.6.1: MD -1.20 mg/dL, 95% CI -1.69 to -0.71). There was no significant difference between study arms in C-reactive protein reported by Ayli 2004 (Analysis 2.6.2: MD -0.4 mg/dL, 95% CI -3.0 to 2.2).

Markers of oxidative stress

Neither Attallah 2006 nor Ayli 2004 reported markers of oxidative stress.

ESA and intravenous iron doses

ESA dose

Attallah 2006 reported ESA was significantly lower in vitamin c group compared to the control group (Analysis 3.1: MD -18 U/kg/wk, 95% CI -35.62 to -0.38). Ayli 2004 did not report data on ESA dose.

Intravenous iron therapy dose

Attallah 2006 reported that there was no significant difference in intravenous iron therapy dose between the study arms (Analysis 3.2: MD -0.20 mg/wk, 95% CI -16.15 to 15.75). Ayli 2004 did not report on intravenous iron therapy dose.

Other outcomes

Hospitalisation days

Neither Attallah 2006 nor Ayli 2004 reported numbers of hospitalisation days.

Quality of life scores

Neither Attallah 2006 nor Ayli 2004 reported quality of life scores.

DISCUSSION

The results of this systematic review highlight the absence of adequately powered randomised controlled trials (RCT) examining the effect of various interventions to treat ESA hyporesponsiveness. We found that there was insufficient and inadequate evidence to recommend any intervention to ameliorate ESA-hyporesponsiveness.

We identified only one RCT that defined ESA-hyporesponsiveness as intravenous EPO dose $\geq$ 450 U/kg/wk (Attallah 2006). When inclusion criteria were extended to include subcutaneous EPO dose $\geq$ 200 U/kg/wk, another study, Ayli 2004, was found to be eligible for inclusion.

In relation to intravenous vitamin C therapy, Attallah 2006 demonstrated increases in haemoglobin, haemoglobin content in reticulocytes, and transferin saturation; and reductions in erythropoietin dose and C-reactive protein. Ayli 2004 reported that use of high-flux dialyser for six months was associated with improvement in haemoglobin, but there was no effect on C-reactive protein or iron studies. Both Attallah 2006 and Ayli 2004 were single-centre studies and included 42 and 48 participants respectively. The studies included only haemodialysis patients, and hence, results may not be generalisable to CKD patients not yet on dialysis, those on peritoneal dialysis, or in settings where patient populations differ.

There is no single widely accepted definition of ESA resistance. KDOQI has defined ESA resistance as failure to achieve haemoglobin 11 g/dL with ESA dose equivalent to epoetin greater than 500 IU/kg/wk (KDOQI 2006). Publication of KDIGO anaemia guidelines is expected this year. As yet, there have been no RCTs performed explicitly in patients with ESA resistance as defined by KDOQI.

In the Normal Haematocrit Cardiac Trial, more participants in the normal haematocrit group reached the primary endpoint (composite of death and non-fatal myocardial infarction) with mean erythropoietin doses of 440 IU/kg/wk, which is lower than the KDOQI definition (Besarab 1998). In the CHOIR trial, it was reported that ESA dose > 20,000 IU/wk was associated with increased risk of death, congestive heart failure, stroke, and myocardial infarction (Szczech 2008).

Several observational studies have suggested a linear association between ESA dose and adverse outcomes (Brookhart 2010; Messana 2009; Regidor 2006; Zhang 2004; Zhang 2009). There is substantial variability in the reporting of ESA dose, such as IU/kg/wk, IU/wk, or ESA dose normalised to haemoglobin level. Therefore, the current KDOQI definition of ESA resistance needs to be revised, and the new definition should be based on ESA-resistance index (ERI) rather than ESA dose to bring uniformity in reporting.

The revised inclusion criteria of the ongoing HERO Study are ESA-resistance index $\geq$ 1.0 IU/kg/wk/haemoglobin for epoetin-treated patients and $\geq$ 0.005 µg/kg/wk/g haemoglobin for darbepoetin-treated patients (Johnson 2008). Table 1 presents current definitions of ESA resistance.

An emerging body of evidence indicates more harm than benefit from targeting higher haemoglobin levels with ESA therapy. Patients who needed higher doses of ESA experienced increased mortality at any haemoglobin level, and patients who achieved target haemoglobin levels had better outcomes than those who did not.

Further RCTs are needed urgently to consider the clinical impacts of therapies purported to reduce ESA resistance.

AUTHORS' CONCLUSIONS

Implications for practice

Based on two small, single-centre studies, there was inadequate evidence to recommend any intervention to ameliorate ESA-hyporesponsiveness.

Implications for research

Adequately powered multicentre RCTs involving a wide range of CKD patients receiving ESA therapy should be conducted as a priority. In addition to those on haemodialysis, future RCTs should include pre-dialysis CKD patients as well people receiving peritoneal dialysis.

Future studies should focus on true ESA responsiveness rather than a haemoglobin-targeted approach. Importantly, these studies should also include cost-effectiveness and economic analyses.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Attallah 2006

Methods	• Study design: RCT • Time frame: NS • Follow-up period: 6 months
Participants	• Country: USA • Setting: large inner-city HD centre • Inclusion criteria: ESKD patients receiving HD therapy for at least 6 months; administered IV EPO ≥ 6 months at dose ≥ 450 U/kg/wk; 3 month average Hb level ≤ 11 g/dL; ferritin level > 500 ng/mL; TSAT ≤ 50% and administered maintenance IV iron • Number (treatment/control): 20/22 • Age (mean ± SD) years: treatment group (50.6 ± 4.7); control group (49.0 ± 5.9) • Sex (M/F): treatment group (9/11); control group (10/12) • Exclusion criteria: bone marrow malignancy; myelodysplastic syndrome; chronic infection; haemochromatosis; haemoglobinopathies; significant bleeding (decrease in Hb > 2 g/L) during the past 3 months; mean corpuscular volume > 100 fL; CRP > 20 mg/dL; Bio-PTH > 500 pg/mL (ng/L); aluminium level > 20 µg/L
Interventions	Treatment group • Vitamin C ○ Dose: 300 mg IV on each dialysis session Control group • No treatment
Outcomes	• Hb level • EPO dose • Iron studies • CRP • Blood transfusion • Hospitalisation
Notes	• Patients were to be withdrawn from the study if they developed bone marrow malignancy, myelodysplastic syndrome, haemochromatosis, or blood loss of ≥ 500 mL during the 6 month study period • Patients on peritoneal dialysis were excluded from the study. • One patient from the control arm was excluded because of significant upper gastrointestinal bleeding

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with blocks of 4

Attallah 2006 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Stated "concealed randomisation was performed using 1:1 allocation ratio with blocks of 4". No further information provided
Blinding (performance bias and detection bias) Participants	High risk	Open-label
Blinding (performance bias and detection bias) Investigators	High risk	Open-label
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up or accounted for at 6 months
Selective reporting (reporting bias)	Unclear risk	Hb changes in individual patient data are presented in figures only. It was unclear how many patients in each arm achieved target Hb
Other bias	High risk	Single-centre study

Ayli 2004

Methods	• Study design: RCT • Time frame: NS • Follow-up period: 6 months
Participants	• Country: Turkey • Setting: single centre • Inclusion criteria: ESKD patients receiving HD; administered SC EPO $\geq$ 6 months at $\geq$ 200 U/kg/wk; Hb level $\leq$ 11 g/dL • Number (treatment/control): 24/24 • Age (mean ± SD) years: treatment group (59.9 ± 14.9); control group (58.3 ± 13.1) • Sex (M/F): treatment group (12/12); control group (14/10) • Exclusion criteria: iron deficiency; chronic blood loss; acute or chronic infection; malnutrition; haemolysis; vitamin B_{12} or folic acid deficiency; haemoglobinopathies; malignancy; treatment with ACEi or ARB
Interventions	Treatment group • Polysulphone high-flux dialyser (Fresenius F60) Control group

Ayli 2004 (*Continued*)

	• Polysulphone low-flux dialyser (Fresenius F6 HPS)
Outcomes	• Hb level • HCT level • EPO dose • Iron studies • CRP • Vitamin B_{12} and folic acid levels • Dialysis adequacy tests (urea reduction ratio and Kt/V urea) • Beta 2 microglobulin
Notes	• Patients on peritoneal dialysis were excluded from the study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) Participants	Unclear risk	Not described
Blinding (performance bias and detection bias) Investigators	Unclear risk	Not described
Blinding (performance bias and detection bias) Outcome assessors	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients were followed up or accounted for at 6 months
Selective reporting (reporting bias)	Unclear risk	Proportion of participants in each arm achieving target haemoglobin is not described. Data on mean EPO dose presented in figure only
Other bias	High risk	Single-centre study, patients on peritoneal dialysis were excluded

ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin-II receptor blocker; CRP - C-reactive protein; DPO - darbepoetin; EPO - erythropoietin; ESKD - end-stage kidney disease; GFR - glomerular filtration rate; Hb - haemoglobin; HCT - haematocrit;

HD - haemodialysis; IV - intravenous; NS - not stated; PTH - parathyroid hormone; RCT - randomised controlled trial; SC - subcutaneous; TSAT - transferin saturation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abe 2010	Study participants did not have ESA resistance.
Acchiardo 1989	Study participants did not have ESA resistance.
Aliev 1997	Study participants did not have ESA resistance.
Andrulli 2010	Study participants did not have ESA resistance.
Ballal 1991	Study participants did not have ESA resistance.
Barany 1998	Study participants did not have ESA resistance.
Berns 1992	Study participants did not have ESA resistance.
Brockenbrough 2006	Study participants did not have ESA resistance.
Buchwald 1977	ESA was not used.
Cao 2010	Study participants did not have ESA resistance.
Caruso 1998	Study participants did not have ESA resistance.
Cerulli 2000	Study participants did not have ESA resistance.
Chan 2005	Study participants did not have ESA resistance.
Chen 2003	Study participants did not have ESA resistance.
Cruz 2008	Not RCT
Culleton 2007	Study participants did not have ESA resistance.
Deira 2003	Study participants did not have ESA resistance.
Di Iorio 2003	Study participants did not have ESA resistance.
ECAP Study 2006	Ineligible patient population
Eiselt 2000	Study participants did not have ESA resistance.

(*Continued*)

Garcia Cortes 1999	Study participants did not have ESA resistance.
Garrote 2009	Ineligible patient population (this study included iron deficient patients who lacked true ESA resistance)
Gastaldello 1995	Not RCT
Gaughan 1997	Study participants did not have ESA resistance.
Giancaspro 2000	Ineligible patient population (this study included iron deficient patients who lacked true ESA resistance)
Hakemi 2005	Study participants did not have ESA resistance.
Hsu 2004	Study participants did not have ESA resistance.
Hung 2005	Study participants did not have ESA resistance.
Imada 2001	Study participants did not have ESA resistance.
ISRCTN96315193	Study participants did not have ESA resistance.
Jacobs 2006	Not RCT
Janssen 1995	Study participants did not have ESA resistance.
Kato 2000	Study participants did not have ESA resistance.
Keven 2003	Study participants did not have ESA resistance.
Klarenbach 2002	Not RCT
Kletzmayr 1999	Study participants did not have ESA resistance.
Koronis 2000	Study participants did not have ESA resistance.
Labonia 1995	Study participants did not have ESA resistance.
Lee 2001	Study participants did not have ESA resistance.
Locatelli 1999	Study participants did not have ESA resistance.
Locatelli 2000	Study participants did not have ESA resistance.
Malegos 2000	Study participants did not have ESA resistance.
Miyahara 1990	Study participants did not have ESA resistance.
Mydlík 2003	Not RCT

(*Continued*)

Nakamoto 2008	Study participants did not have ESA resistance.
Navarro 2002	ESA not used in the control arm (compared erythropoietin to androgens)
Odabas 2003	Study participants did not have ESA resistance.
Ono 1992	Study participants did not have ESA resistance.
Onoyama 1989	Study participants did not have ESA resistance.
Opatrnì 1998	Study participants did not have ESA resistance.
Panichi 2011	Study participants did not have ESA resistance.
Rao 2003	Not RCT
Richardson 2003	Study participants did not have ESA resistance.
Saxena 1997	Study participants did not have ESA resistance.
Sezer 2002	Study participants did not have ESA resistance.
Shahrbanoo 2008	Study participants did not have ESA resistance.
Sheashaa 2005	Study participants did not have ESA resistance.
Sorge-Haedicke 2001	Study participants did not have ESA resistance.
Taji 2004	Study participants did not have ESA resistance.
Tarng 1998	Study participants did not have ESA resistance.
Tarng 1999	Study participants did not have ESA resistance.
Tarng 2004	Study participants did not have ESA resistance.
Ursea 1995	Study participants did not have ESA resistance.
Usberti 2002a	Study participants did not have ESA resistance.
Usberti 2002b	Study participants did not have ESA resistance.
Vaslaki 2006	Study participants did not have ESA resistance.
Wang 2000	Study participants did not have ESA resistance.

(*Continued*)

Yang 2006	Study participants did not have ESA resistance.

ESA - Erythropoiesis-simulating agents; RCT - randomised control trial

Characteristics of ongoing studies *[ordered by study ID]*

Johnson 2008

Trial name or title	The Hemoglobin elevation in Erythropoietin Resistance with Oxpentifylline (HERO Study)
Methods	Investigator-initiated, prospective, double-blind, randomised, placebo-controlled phase 3 trial
Participants	Inclusion criteria • Adults aged ≥18 years with CKD stage 4 or 5 (on dialysis or eGFR < 30 mL/min/1.73 m²) able to give informed consent and who have Hb concentration < 110 g/L for at least 3 months in spite of EPO dose ≥ 200 IU/kg/wk or DPO dose ≥ 1 μg/kg/wk for at least 1 month. Revised criteria based on ESA-resistance index ≥ 1.0 IU/kg/wk/g Hb for epoetin-treated patients and ≥ 0.005 μg/kg/wk/g Hb for DPO-treated patients. Exclusion criteria • Patients with a history of psychological illness or condition which interferes with their ability to understand or comply with the requirements of the study • Pregnancy or breastfeeding • Known hypersensitivity to, or intolerance of, oxpentifylline or other methylxanthines, such as caffeine, theophylline or theobromine • Active peptic ulcer disease • Absolute or functional iron deficiency (ferritin < 100 μg/L and/or TSAT < 20%) • Vitamin B_{12} or folate deficiency • PTH > 100 pmol/L • Serum aluminium > 2 μmol/L • Urea reduction ratio < 65% or single pool Kt/V < 1.0 (HD patients) or total weekly Kt/V < 1.7 (PD patients) • Presence of systemic haematological disease (including antibody-mediated pure red cell aplasia) or known haemoglobinopathy • Major surgery, infection, acute myocardial infarction or malignancy within the last 3 months • Melatonin treatment, androgen therapy or blood transfusion within the previous month • Vitamin C therapy > 100 mg/d or at a dose that has changed within the last 3 months • Haemorrhagic stroke or severe haemorrhage within the last 3 months.
Interventions	Intervention arm • Oxpentifylline 400 mg once daily Control arm • Identical placebo 1 tablet once daily
Outcomes	Primary: difference in Hb concentration between the oxpentifylline and control groups at the end of the 4 month study period

Johnson 2008 (*Continued*)

Starting date	April 2008
Contact information	Professor David Johnson, Level 2 ARTS Building, Princess Alexandra Hospital, Woolloongabba 4102 Queensland, Australia Tel: 61-7-31765080, Fax: 61-7-31765480, Email: David_Johnson@health.qld.gov.au
Notes	

NCT01526798

Trial name or title	Improvement of EPO-resistance in Hemodialysis Patients With Chronic Inflammation by High Cut-off Hemodialysis (CIEPO-PILOT)
Methods	Open-label RCT
Participants	Inclusion criteria • ESKD treated with chronic HD for at least 3 months • Treatment with high-flux dialyzers for at least 3 months • Age ≥18 years • Receiving ESA to treat anaemia for at least 3 months • Impaired ESA responsiveness as indicated by EPO resistance index > median of patients in study centre • TSAT ≥ 20% (last routine value prior to randomisation) • Serum ferritin ≥ 100 ng/mL (last routine value prior to randomisation) Exclusion criteria • Acute infection ≤ 4 weeks prior to randomisation • HIV or hepatitis infection • Catheter • Chronic liver disease • Active cancer • Known blood dyscrasia (paraprotein abnormalities) • Known bleeding disorders • Bleeding episode ≤ 12 weeks prior to randomisation • Blood/red cell transfusion ≤ 12 weeks prior to randomisation • Hypoalbuminaemia defined as serum albumin concentration below 35 g/L (last routine value prior to randomisation) • Participation in another clinical interventional investigation • Pregnancy • Inability to give informed consent • Planned transplantation within study period + 3 months • Planned interventions requiring hospitalisation >1 week
Interventions	Intervention arm: Device: Theralite (high cut-off HD), HD with Theralite dialyzer alternating with standard high-flux dialyzer (Polyflux H) Control arm: Device: Polyflux H, Conventional high-flux dialyzer
Outcomes	EPO resistance index
Starting date	March 2012

NCT01526798 (*Continued*)

Contact information	Dr. Ugo Teatini, Azienda Ospedaliera Garbagnate Milanese Ospedale Bollate - Divisione Nefrologia e Dialisi, Bollate, Milan, Italy, 20021
Notes	

CKD - chronic kidney disease; DPO - darbepoetin; EPO - erythropoietin; eGFR - estimated glomerular filtration rate; ESA - erythropoiesis-stimulating agent; Hb - haemoglobin; HD - haemodialysis; PD - peritoneal dialysis; PTH - parathyroid hormone; RCT - randomised controlled trial; TSAT - transferrin saturation

DATA AND ANALYSES

Comparison 1. Clinical outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-fatal cardiovascular events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Hospitalisations	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Haematology and biochemistry results

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Vitamin C versus control	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 High-flux versus low-flux dialyser	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Transferin saturation (TSAT)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Vitamin C versus control	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 High-flux versus low-flux dialyser	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Ferritin	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Vitamin C versus control	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 High-flux versus low-flux dialyser	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Haemoglobin content in reticulocytes (CHr)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 C-reactive protein	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Vitamin C versus control	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 High-flux versus low-flux dialyser	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. ESA and IV iron doses

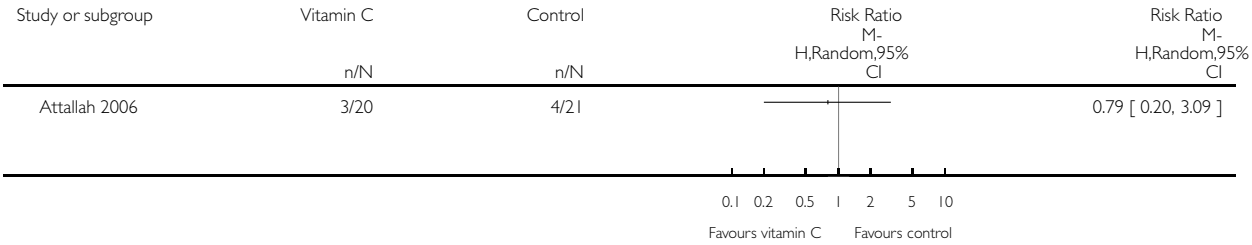
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 EPO dose	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 IV Iron	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Clinical outcomes, Outcome 1 Non-fatal cardiovascular events.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 1 Clinical outcomes

Outcome: 1 Non-fatal cardiovascular events

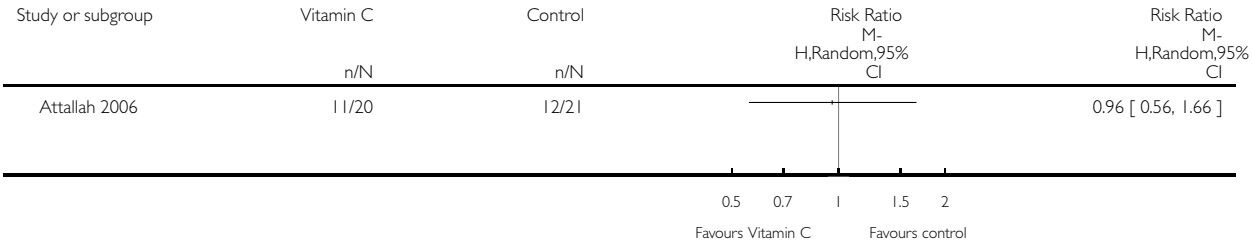


Analysis 1.2. Comparison 1 Clinical outcomes, Outcome 2 Hospitalisations.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 1 Clinical outcomes

Outcome: 2 Hospitalisations



Analysis 2.1. Comparison 2 Haematology and biochemistry results, Outcome 1 Haemoglobin.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 1 Haemoglobin

Study or subgroup	Treatment N	Mean(SD)[g/dL]	Control N	Mean(SD)[g/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Vitamin C versus control						
Attallah 2006	20	10.5 (0.9)	21	9.6 (0.8)		0.90 [0.38, 1.42]
2 High-flux versus low-flux dialyser						
Ayli 2004	24	11.4 (0.5)	24	9.5 (0.4)		1.90 [1.64, 2.16]

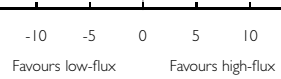
Analysis 2.2. Comparison 2 Haematology and biochemistry results, Outcome 2 Haematocrit.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 2 Haematocrit

Study or subgroup	High-flux dialyser N	Mean(SD)[%]	Low-flux dialyser N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Ayli 2004	24	35.8 (2.1)	24	29 (1.9)		6.80 [5.67, 7.93]



Analysis 2.3. Comparison 2 Haematology and biochemistry results, Outcome 3 Transferin saturation (TSAT).

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 3 Transferin saturation (TSAT)

Study or subgroup	Treatment N	Mean(SD)[%]	Control N	Mean(SD)[%]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Vitamin C versus control						
Attallah 2006	20	37.3 (3)	21	29.3 (2.8)		8.00 [6.22, 9.78]
2 High-flux versus low-flux dialyser						
Ayli 2004	24	35.8 (9.6)	24	34.5 (9.1)		1.30 [-3.99, 6.59]

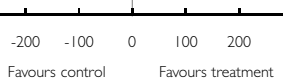
Analysis 2.4. Comparison 2 Haematology and biochemistry results, Outcome 4 Ferritin.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 4 Ferritin

Study or subgroup	Treatment N	Mean(SD)[ng/mL]	Control N	Mean(SD)[ng/mL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Vitamin C versus control						
Attallah 2006	20	732 (149)	21	724 (156.5)		8.00 [-85.51, 101.51]
2 High-flux versus low-flux dialyser						
Ayli 2004	24	267 (73)	24	270 (70)		-3.00 [-43.46, 37.46]



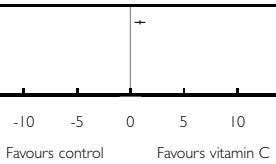
Analysis 2.5. Comparison 2 Haematology and biochemistry results, Outcome 5 Haemoglobin content in reticulocytes (CHr).

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 5 Haemoglobin content in reticulocytes (CHr)

Study or subgroup	Vitamin C N	Mean(SD)[pg]	Control N	Mean(SD)[pg]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Attallah 2006	20	30.7 (0.9)	21	29.8 (0.7)		0.90 [0.40, 1.40]



Analysis 2.6. Comparison 2 Haematology and biochemistry results, Outcome 6 C-reactive protein.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 2 Haematology and biochemistry results

Outcome: 6 C-reactive protein

Study or subgroup	Treatment N	Mean(SD)[mg/dL]	Control N	Mean(SD)[mg/dL]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Vitamin C versus control						
Attallah 2006	20	0.9 (0.3)	21	2.1 (1.1)		-1.20 [-1.69, -0.71]
2 High-flux versus low-flux dialyser						
Ayli 2004	24	6.3 (4.5)	24	6.7 (4.7)		-0.40 [-3.00, 2.20]

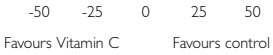
Analysis 3.1. Comparison 3 ESA and IV iron doses, Outcome 1 EPO dose.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 3 ESA and IV iron doses

Outcome: 1 EPO dose

Study or subgroup	Vitamin C		Control		Mean Difference	Mean Difference
	N	Mean(SD)[IU/kg/wk]	N	Mean(SD)[IU/kg/wk]	IV,Random,95% CI	IV,Random,95% CI
Attallah 2006	20	429 (24.7)	21	447 (32.5)		-18.00 [-35.62, -0.38]



Analysis 3.2. Comparison 3 ESA and IV iron doses, Outcome 2 IV Iron.

Review: Interventions for erythropoietin-resistant anaemia in dialysis patients

Comparison: 3 ESA and IV iron doses

Outcome: 2 IV Iron

Study or subgroup	Vitamin C		Control		Mean Difference	Mean Difference
	N	Mean(SD)[mg/wk]	N	Mean(SD)[mg/wk]	IV,Random,95% CI	IV,Random,95% CI
Attallah 2006	20	26.6 (25.4)	21	26.8 (26.7)		-0.20 [-16.15, 15.75]

ADDITIONAL TABLES

Table 1. Current definitions of ESA resistance

Author/study	Definition of ESA resistance
KDOQI (KDOQI 2006)	Epoetin dose > 500 IU/kg/wk
Normal Haematocrit Cardiac Trial (Besarab 1998)	Epoetin dose 440 IU/kg/wk in the normal haematocrit group
CHOIR study (Szczech 2008)	Epoetin dose > 20,000 IU/wk
Attallah 2006	Epoetin dose > 450 IU/kg/wk (IV)
Ayli 2004	Epoetin dose > 200 IU/kg/wk (SC)
Johnson 2008; HERO Study	Epoetin dose ≥ 200 IU/kg/wk or darbepoetin dose ≥ 1 μg/kg/wk
HERO Study (revised criteria)	ESA-resistance index (ERI) ≥ 1.0 IU/kg/wk/g Hb for epoetin-treated patients and ≥ 0.005 µg/kg/wk/g Hb for darbepoetin-treated patients

Hb - haemoglobin

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. dialysis:ti,ab,kw 2. (hemodia* or haemodia*):ti,ab,kw 3. (hemofiltration or haemofiltration):ti,ab,kw 4. (#1 OR #2 OR #3) 5. an*emia:ti,ab,kw 6. "iron overload":ti,ab,kw 7. (#5 OR #6) 8. erythropo*etin:ti,ab,kw 9. (erythropo*esis next stimulating next agent*):ti,ab,kw 10. (continuous next erythropo*esis next receptor next activator*):ti,ab,kw 11. EPO:ti,ab,kw 12. rhEPO:ti,ab,kw 13. epo*etin:ti,ab,kw 14. Eprex:ti,ab,kw

(*Continued*)

	15. Epogen:ti,ab,kw 16. Procrit:ti,ab,kw 17. darbepo*etin:ti,ab,kw 18. aranesp:ti,ab,kw 19. neorecormon:ti,ab,kw 20. CERA:ti,ab,kw 21. mircera:ti,ab,kw 22. (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) 23. (#4 AND #7 AND #22)
MEDLINE	1. exp Renal Dialysis/ 2. dialysis.tw. 3. (hemodialysis or haemodialysis).tw. 4. (hemofiltration or haemofiltration).tw. 5. (hemodiafiltration or haemodiafiltration).tw. 6. or/1-5 7. Anemia/ 8. Anemia,Refractory/ 9. Iron Overload/ 10. (an?emia or an?emic).tw. 11. or/7-10 12. exp Erythropoietin/ 13. erythropoiesis stimulating agent$.tw. 14. erythropo?etin.tw. 15. EPO.tw. 16. rhEPO.tw. 17. epo?etin.tw. 18. Eprex.tw. 19. Epogen.tw. 20. Procrit.tw. 21. darbepo?etin.tw. 22. aranesp.tw. 23. neorecormon.tw. 24. continuous erythropo?esis receptor activator.tw. 25. CERA.tw. 26. Mircera.tw. 27. or/12-26 28. and/6, 11, 27
EMBASE	1. Anemia/ 2. Refractory Anemia/ 3. Iron Overload/ 4. (an?emia or an?emic).tw. 5. or/1-4 6. Erythropoietin/ 7. Recombinant Erythropoietin/ 8. erythropo?esis stimulating agent$.tw. 9. erythropo?etin.tw.

(*Continued*)

	10. EPO.tw. 11. rhEPO.tw. 12. epo?etin.tw. 13. Eprex.tw. 14. Epogen.tw. 15. Procrit.tw. 16. darbepo?etin.tw. 17. aranesp.tw. 18. neorecormon.tw. 19. continuous erythropo?esis receptor activator.tw. 20. CERA.tw. 21. Mircera.tw. 22. or/6-21 23. exp Renal Replacement Therapy/ 24. dialysis.tw. 25. (hemodialysis or haemodialysis).tw. 26. (hemofiltration or haemofiltration).tw. 27. (hemodiafiltration or haemodiafiltration).tw. 28. or/23-27 29. and/5, 22, 28

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed en-

(*Continued*)

	velopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in

(*Continued*)

	means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem

(*Continued*)

	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

- Write the protocol: SB, DF, EB, CH, DJ, IM, AC, VP
- Study selection: SB, CH, DJ
- Extract data from studies: SB, DJ
- Enter data into RevMan: SB, DJ
- Data analysis: SB, DF, EB
- Interpret the analysis: SB, DJ
- Draft the final review: SB, DJ
- Disagreement resolution: DF, EB, CH, IM, AC, VP
- Update the review: SB, DJ

DECLARATIONS OF INTEREST

- Dr Sunil V Badve, Elaine Beller and Daniel P Francis have no conflicts of interest to declare.

- Associate Professor Carmel Hawley has received consulting fees from Amgen and Janssen-Cilag; research grants from Amgen, Roche and Janssen-Cilag; and speakers' honoraria from Amgen.

- Professor Alan Cass is the recipient of a NHMRC Senior Research Fellowship. He has received speaker's honoraria and research grants from Janssen-Cilag, Amgen and Roche.

- Associate Professor Vlado Perkovic has received speakers' honoraria from Roche and research grants from Johnson and Johnson Pharmaceutical Research & Development and Roche.

- Professor Iain C. Macdougall has received consultant fees, research grants, and/or lecture fees from Amgen, Ortho biotech, Roche, Affymax, Takeda, Hospira, and Sandoz.

- Professor David Johnson has received speakers' honoraria, consultancy fees and research grants from Janssen-Cilag, Amgen and Roche. He has received fees for organising education from Amgen and Janssen-Cilag. He has received consultancy fees from Pfizer. He is also the Principal Investigator in the HERO Trial, a randomised, double-blind, placebo-controlled trial of oxpentifylline in the treatment of erythropoietin stimulating agent hyporesponsiveness. Professor Alan Cass and Associate Professor Carmel Hawley are the members of the Trial Management Committee of the HERO trial.

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Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol for this review, we had planned that one of our inclusion criteria would define ESA resistance. Evidence of ESA-resistance, defined as failure to achieve or maintain target range haemoglobin/haematocrit levels in spite of appropriate doses of the ESA (erythropoietin dose $\geq$ 450 U/kg/wk intravenous administration or $\geq$ 300 U/kg/wk for subcutaneous administration or darbepoetin dosage $\geq$ 1.5 µg/kg/wk) (KDOQI 2001; Locatelli 2004) was to be applied. This inclusion criterion was amended because only one eligible study was found.

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Anemia [blood; *drug therapy]; Drug Resistance; Erythropoiesis [*drug effects]; Erythropoietin [*administration & dosage]; Hematocrit; Kidney Failure, Chronic [*complications; therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans